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Langerhans Cell Histiocytosis: An Exploratory Epidemiologic Study of 177 Cases

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There is little information available regarding epidemiologic risk factors for Langerhans cell histiocytosis (LCH). An exploratory investigation was conducted using information obtained from parents of 177 cases of LCH diagnosed before 21 years of age (median 2 years). Utilizing data available from the Children's Cancer Group, LCH cases were compared to two matched control groups including 614 patients diagnosed with a variety of childhood cancers and 318 community controls. Questionnaire data included information on demographics, prenatal and perinatal factors, complications in the neonatal period, environmental exposures, family medical history, and childhood exposures. Factors found to be statistically significantly associated with an increased risk of LCH included: maternal urinary tract infection during the index pregnancy, feeding problems during infancy, and blood transfusions during infancy. Use of supplemental vitamins was associated with a significantly decreased risk of LCH. Results from this exploratory study provide a basis for speculation on potential etiologic risk factors for LCH. Future epidemiologic investigations of LCH need to consider the presenting disease characteristics in assessing possible etiologic factors. **Med. Pediatr. Oncol. 28:92–97**

Key words: Langerhans cell histiocytosis; epidemiology; risk factors

INTRODUCTION

Langerhans cell histiocytosis (LCH), previously referred to as histiocytosis X [1], is a disorder characterized by tissue infiltration with cells of the monocyte/macrophage lineage. Although LCH was first described by Hand in 1893 [2], little is known about its etiologic and epidemiologic features. The annual incidence rate for LCH in children is 4 per million population [3]. Some series have reported a slightly higher incidence in males than in females [4–6]. Systemic disease occurs predominantly in younger children with 60–70% of cases reported before 2 years of age [7,8]. Disease confined to the bone tends to occur at a later age but 50% are diagnosed prior to age 5 [9].

Within the literature there are reports of affected sibling pairs [10] and congenital LCH [11]. Various immunologic abnormalities have been reported including hypergammaglobulinemia [12], chemotactic defects [13], and suppressor cell dysfunction [14]. Earlier LCH was hypothesized to be a lipid disorder and a neoplastic process but these hypotheses are currently not widely accepted [15]. Recent studies have provided evidence that LCH is probably a clonal neoplastic disorder with variable biologic behavior [16]. This report represents the largest case-control study to date designed to evaluate possible risk factors for LCH. The associations explored in this study were factors relating to sociodemographic characteristics, events during pregnancy and birth, exposures during the pregnancy, family medical history, patient's health and development, and the patient's home environment.

MATERIALS AND METHODS

Cases

For this study, cases were ascertained from two sources. Two hundred patients (diagnosed at the respective institutions by the institutional pathologist) with a diagnosis of LCH prior to 21 years of age were identified through the University of Minnesota, Children's Hospital of Philadelphia, Mayo Clinic, and the University of Wisconsin. Cases were diagnosed between January 1971 and May 1986. Clinical data were abstracted from the case's chart by the respective institution. Parents

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of cases were sent a self-administered questionnaire utilized in the Children's Cancer Group (CCG) E04 protocol to assess potential risk factors for childhood cancer. If no response was received, two additional mailings were attempted which resulted in 144 (72%) completed questionnaires, with the other 56 cases having become lost to follow-up or failing to respond to our mailings. The second source of cases consisted of the 33 LCH patients entered into the CCG-E04 protocol. Clinical data were not available for the 33 CCG-E04 LCH cases. In total, there were 177 case questionnaires available for analysis.

Controls

Two matched control groups were utilized in this study and included: 1) A cancer control group selected from 1,828 patients diagnosed with a variety of childhood cancers at 25 CCG institutions participating in the E04 study, and 2) a community control group based on 799 subjects identified through a random digit dialing procedure [17] for case-control studies conducted within the CCG.

LCH cases were matched with the controls on date of birth ($\pm$2 years), race (white vs. nonwhite), geographic region (six regions), and annual family income category ($<$\$7,500, \$7,500–15,000, \$15,000–30,000, \$30,000–50,000, $>$\$50,000). A variable matching ratio was used, with a maximum of four controls per case where possible.

Questionnaire

The CCG-E04 study consisted of a 22-page questionnaire completed by parents of newly diagnosed cases. The questionnaire obtained information on medical and environmental exposures to the index child as well as to the parents, the pregnancy and birth of the index child, and a detailed family history. Details regarding the CCG-E04 study have been previously reported [18]. All responses were computer-entered and maintained in a database using the statistical package Epilog Plus [19].

Analysis

Conditional logistic regression was used to estimate relative risks (RR), 95% confidence intervals (CI), and significance levels (P) [20]. Stepwise regression was used, and the criteria for keeping variables in the final model were based on the statistical significance.

RESULTS

Clinical Features

Clinical information was available on 144 LCH cases ascertained from the four primary contributing centers. Table I shows selected demographic features of the three study groups. LCH was diagnosed before the age of 3 years in 57% of cases, between 3–6 years in 18%, 7–9 years in 11%, and greater than or equal to 10 years in 13%. The most frequently affected sites included bone (74%), skin (38%), lymph nodes (14%), liver (13%), central nervous system (CNS; 12%), bone marrow (10%), and lungs (10%). Sixty-two percent of the LCH cases had only a single site affected while 38% had a disseminated form of the disease involving two to seven sites. Of the 90 cases having single-site involvement, 14% involved the skin only and 80% the bone. Of the cases with only skin involvement, 77% were less than 3 years of age whereas only 33% of cases with only bone involvement were under 3 years of age.

Of the 54 cases with disseminated disease, 64% had LCH involvement of the bone, 75% skin, and 46% had both skin and bone. Seventy-seven percent of the cases with disseminated disease were less than 3 years of age.

Demographic Features

The ratio of males to females was similar in the LCH cases, cancer controls, and community controls (1.4:1, 1.4:1, and 1.1:1, respectively). Maternal age at the birth of the index child was similar among the three groups (Table I). However, it was noted that all of the five LCH cases having a mother 41 years or older at the time of birth were diagnosed at less than 2 years of age and had the disseminated form of the disease.

Since the matching criteria included income, it was anticipated that the three comparison groups would likely be comparable on a variety of demographic factors. No statistically significant differences were noted in family size, parental education, type of domicile, residential area, exposures to water pollution, air pollution, and pets.

Prenatal and Perinatal Factors

Parents of LCH cases and the controls reported similar patterns of use of cigarettes, caffeinated and decaffeinated coffee, and alcohol prior to and during pregnancy with the index child. There were no statistically significant differences in the reported frequencies of maternal infections during or immediately after pregnancy, including rubella, measles, mumps, influenza, mononucleosis, genital herpes, varicella, and rheumatic fever. Maternal urinary tract infections were reported more often for LCH compared to community controls (RR = 2.64, 95% CI, 1.27–5.48, $P = 0.009$) and cancer controls (RR = 1.92, 95% CI, 1.09–3.36, $P = 0.02$).

Maternal medication use, prior to or during pregnancy, did not reveal any statistically significant association with LCH risk. This included use of oral contraceptives, hormonal preparations, tranquilizers, analgesics, diet pills, antibiotics, vitamins, pregnancy tests, recreational drugs, antiemetics, and clonidine. History of infertility was similar for the parents of all three groups.

TABLE I. Distribution of Selected Demographic Characteristics

	LCH cases (n = 177) (%)	Community controls (n = 318) (%)	Cancer controls (n = 614) (%)
Sex			
Males	58	52	58
Females	42	48	42
Age at diagnosis (years)			
<1	23	—	8
1–2	34	—	19
3–6	18	—	30
7–9	11	—	20
10–14	12	—	13
>14	2	—	10
Family size (no. of live births)			
1	20	29	19
2–4	74	65	73
>4	6	6	8
Maternal age at birth (years)			
<21	13	17	17
21–25	36	35	34
26–30	30	29	29
31–35	11	12	14
36–40	5	5	4
>41	5	2	2

The reported occurrence of pregnancy-related events including spotting, fluid retention, x-ray exposure, general anesthesia, amniocentesis, and cesarean section was not different for LCH cases and controls. Similarly, breast feeding and neonatal problems of jaundice, diarrhea, and infections showed no association for the development of LCH.

Infancy

Feeding problems in the first 6 months were reported in 20.2% of LCH cases vs. 10.3% of community controls (RR = 2.44, 95% CI, 1.12–5.31, $P = 0.02$) and 13.8% of cancer controls (RR = 1.51, 95% CI, 0.84–2.73, $P = 0.2$). No associations were observed for receiving ultraviolet light or oxygen therapy in the neonatal period and the development of LCH. LCH cases more frequently received medications during infancy than community controls (25% of the LCH compared to 12% of the normal controls, RR = 4.46, 95% CI, 1.98–10.07, $P = 0.0001$) and cancer controls (RR = 2.1, 95% CI, 1.17–3.76, $P = 0.01$). Medications most commonly reported for all groups were antibiotics, with penicillin being the most frequently reported.

The incidence of blood transfusions during the first 6 months of life was significantly higher in LCH than in the community control group (RR = 12.1, 95% CI, 1.3–115.3, $P = 0.009$).

Environmental Exposures

In general, RR estimates tended to be higher when comparing LCH to community controls than to cancer controls (Table II). Exposure to solvents showed a high RR when compared to community controls but this decreased both in magnitude and significance when compared to cancer controls. Gasoline exposure displayed an increased but not significant RR for community controls but displayed a risk below one for cancer controls. Radiation exposure of the mother and father showed a protective effect against the development of LCH.

Family Medical History

There were no reports of LCH in family members (first-degree relatives and grandparents) of cases. The reported occurrence of cancer was similar in family members for LCH cases and controls. Benign tumors or cysts were reported significantly more often in LCH family members than in family members of the community control group (RR = 2.07, 95% CI, 1.18–3.65, $P = 0.01$) but not in cancer controls. Family or subject history of blood disorders, thyroid disorders, allergy, psychological disorders, or lung disease showed no significant association with an increased risk of LCH.

Childhood Exposures

Childhood infections of varicella, rheumatic fever, cold sores, hepatitis, Epstein-Barr virus, measles, mumps, and rubella were not associated with an increased risk of LCH. Vaccinations for measles, mumps, and rubella were not associated with the development of LCH. No significant association was found with appendectomy or tonsillectomy.

No statistically significant association was found be-

TABLE II. RR Estimates for Certain Parental Exposures

	Mother		Father	
Risk factors	Cancer RR# (95% CI)	Community RR (95% CI)	Cancer RR (95% CI)	Community RR (95% CI)
Chemicals/solvents	1.2 (0.5–2.9)	2.6 (0.8–8.5)	0.9 (0.5–1.8)	1.9 (0.9–4.4)
Paints, lacquers, stains	1.1 (0.5–2.5)	0.7 (0.2–2.2)	1.2 (0.7–2.1)	1.3 (0.6–2.7)
Radiation	0.6 (0.3–1.0)	0.6 (0.3–1.4)	0.5 (0.2–0.9)	0.6 (0.2–1.6)
Plastic or resin fumes	0.3 (0.03–3.1)	—	1.3 (0.6–2.9)	1.9 (0.6–6.1)
Gases	0.3 (0.1–1.3)	1.6 (0.1–21.9)	0.6 (0.2–1.6)	3.2 (1.0–10.1)
Engine exhaust fumes	0.8 (0.3–2.3)	0.5 (0.1–2.5)	0.8 (0.4–1.6)	1.1 (0.5–2.5)
Petroleum products	2.9 (0.9–9.1)	0.4 (0.1–2.4)	1.2 (0.6–2.2)	1.6 (0.7–3.8)
Dusts	0.9 (0.5–1.9)	1.6 (0.6–4.2)	0.95 (0.6–1.6)	2.2 (1.04–4.8)
Dyes	0.6 (0.3–1.4)	0.8 (0.3–2.1)	2.4 (0.6–9.0)	3.1 (0.5–21.5)
Metals	1.1 (0.2–7.5)	1.0 (0.1–9.4)	0.6 (0.2–1.6)	0.6 (0.2–1.9)
Insecticides or herbicides	1.0 (0.4–2.4)	1.1 (0.3–4.2)	0.8 (0.4–1.6)	1.7 (0.6–4.6)
Farm animals	1.4 (0.8–2.7)	2.5 (1.0–6.0)	1.0 (0.6–1.8)	2.9 (1.3–6.7)
Cleaning compounds	1.4 (0.8–2.7)	1.3 (0.6–2.8)	1.3 (0.6–2.7)	1.5 (0.5–4.4)

tween LCH and the use of antibiotics, tranquilizers, antihypertensives, anti-inflammatory agents, hormones, allergy medication, oral contraceptives, and recreational drugs. Vitamin use was lower in LCH cases compared to community (RR = 0.58, 95% CI, 0.33–1.03, $P = 0.05$) and cancer controls (RR = 0.65, 95% CI, 0.4–1.03, $P = 0.03$).

Multivariate Analysis

A series of logistic regression analyses were performed using those factors which were found to be statistically significantly associated with LCH risk in the univariate analysis. When comparing LCH cases and cancer controls, the factors which were independently associated with risk of LCH included family history of benign tumors (RR = 1.8, $P = 0.03$). Regression models comparing LCH cases and community controls demonstrated that the risk of LCH was independently associated with family history of benign tumors (RR = 4.4, $P < 0.001$) and history of feeding problems in infancy (RR = 3.4, $P = 0.04$).

DISCUSSION

To our knowledge, this study represents the first analytic epidemiologic investigation in LCH, a disease which is now generally considered not to represent malignancy. This study was initiated as an exploratory investigation of LCH since no specific etiologic factors have been identified. Areas of speculation on the possible etiology of LCH have focused on factors associated with genetics, prenatal events and infection, occurrence of the disease in neonates, and identified immunologic abnormalities. Given the paucity of etiologic information in the literature, the findings of this study will be discussed relative to the three aforementioned areas, while recognizing that possible explanations for the associations observed are highly speculative.

The age and sex distribution of LCH cases in our study is similar to that of other reported case series [21,22]. Moreover, as in other reports [4–6], LCH cases demonstrated a slight male predominance, and appeared to be quite similar with respect to most sociodemographic factors. Clinical features were similar to previously reported case series [4–6,23].

Passage of maternal lymphocytes to the fetus has been suggested as a possible mechanism for the production of histiocytic illness [24]. The findings of a higher frequency of reported urinary tract infections during pregnancy may reflect a situation which would facilitate maternal transfer of lymphocytes. Moreover, the 12-fold risk estimate for LCH (when compared to community controls) associated with blood transfusion during the first 6 months of life may be comparable with transfer of antigenic factors. The lack of a significant association with blood transfusions when LCH cases were compared to childhood cancer controls suggests either an increased frequency of transfusions to be associated with childhood cancers or a possible reporting bias between parents of LCH and cancer parents compared to community controls.

Cigarette smoking has been associated with the development of pulmonary histiocytosis in adults [25]. The lack of an association when compared with the two control groups suggests that in utero exposure to cigarette smoke is not a strong risk factor for LCH in childhood.

When assessing postnatal events during the first 6 months of life, feeding difficulties, increased use of medications, and transfusions must be viewed within the context of the possible influence of the subclinical LCH. Feeding problems could be the result of an ill infant while an increased likelihood of blood transfusions and medication exposure could be explained by the underlying disease.

Because this study assessed a relatively large number of factors, the possibility of multiple comparisons resulting in chance associations must be considered. Moreover, reporting bias is almost always a concern in case-

control studies involving children with a severe chronic disease. This study has the benefit of two control groups, one of which includes children with cancer. LCH and childhood cancer groups should be subject to similar recall by parents. However, if childhood cancer in general were to share any risk factors in common with LCH, associations would not be apparent. These possible methodologic limitations notwithstanding, there are a number of findings (both positive as well as some of those which were negative) from this study which warrant confirmation in future studies. Most notable are the findings of an increased risk with solvent exposure, family history of benign tumors, urinary tract infections during pregnancy, and postnatal blood transfusions.

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